Vitamin E and Prostate Cancer: Current Evidence and Future Directions

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Abstract: Vitamin E has been hypothesized to protect against prostate cancer. The anti-carcinogenic activity of vitamin E is attributed in large part to its potent antioxidant activity - it is the major hydrophobic chain-breaking antioxidant that protects membrane lipids from oxidation. In addition, vitamin E has several important non-antioxidant functions, including inhibition of protein kinase C (PKC) activity, which plays an important role in proliferation, adhesion, immune response, free radical production, and gene expression. Vitamin E also appears to interfere with hormone signaling, which is particularly relevant to prostate carcinogenesis. The concept that common SNPs in genes encoding for proteins responsible for uptake, transport, and delivery of tocopherols and tocotrienols to the prostate may impact upon prostate cancer risk has not been examined and warrants future research. Overall, substantial evidence from mechanistic studies shows a protective effect of vitamin E on prostate carcinogenesis. However, results from observational epidemiologic studies regarding the association between vitamin E and prostate cancer risk are mixed. The available data suggest that vitamin E may more strongly protect against advanced than early-stage prostate cancer, and that the apparent beneficial effect of vitamin E on prostate cancer may be more pronounced among cigarette smokers. At present, the most prudent strategy for prostate cancer prevention regarding vitamin E intake is to adhere to the current U.S. dietary guidelines, which recommend eating a well-balanced diet that is rich in a variety of fruits, vegetables, and whole grains.

STRUCTURE OF VITAMIN E

Vitamin E is a fat-soluble vitamin that occurs naturally in eight different forms, including four tocopherols (α-, β-, γ-, δ-) and four tocotrienols (α-, β-, γ-, δ-). All tocopherols have a long, saturated phytyl side chain, with differences between them arising from the number and position of methyl groups on the chromanol ring. Tocotrienols have an unsaturated side chain, but are otherwise identical to their corresponding tocopherols. Each of the four tocopherols, including α-tocopherol, has eight possible stereoisomer forms due to the presence of three optically active sites, each with two possible configurations (R and S). However, the RRR-stereoisomer is the only form that occurs naturally in plant foods. Most forms of synthetic vitamin E, which are included in fortified foods and vitamin supplements, contain equal amounts of all eight stereoisomers, although the 2R-forms (RRR-, RSR-, RRS-, RSS-) are the only ones that are maintained in human plasma and tissues [1].

VITAMIN E REQUIREMENTS AND INTAKE

In 2000, the recommended dietary allowance (RDA) for vitamin E, which is set to cover the nutrient needs of 97% - 98% of the population, was increased from 10 mg/day (all forms, adjusted for bioavailability) to 15 mg/day (α-tocopherol; 2R- stereoisomeric forms only) for adults 19 years of age and older [1]. Data from two national surveys – the Continuing Survey of Food Intakes by Individuals (CSFII) and the National Health and Nutrition Examination Survey (NHANES III) – indicate, however, that the majority of the U.S. population consumes far less than the recommended amount of vitamin E [2, 3]. Furthermore, according to NHANES III, approximately 30% of the U.S. population has low serum α-tocopherol concentrations (<20 μmol/liter) [4]. Of particular note is that more than 40% of African-American men, but only 27% of white men, have low serum vitamin E levels – an intriguing finding considering that U.S. blacks have disproportionately higher rates of prostate cancer than U.S. whites.

DIETARY SOURCES OF VITAMIN E

The major dietary sources of vitamin E in the U.S. include vegetable oils (corn, soybean, and safflower), products derived from vegetable oils (margarine and vegetable shortening), whole grains, nuts, and wheat germ. Vitamin E is also found in spinach, turnip greens, red peppers, and broccoli, although in relatively small amounts [5]. Individual food items typically contain varying amounts of vitamin E forms. For example, corn and soybean oils each contain 10 times more γ-tocopherol than α-tocopherol, whereas safflower and olive oils are much richer in α-tocopherol [6] .

MECHANISMS OF ACTION OF VITAMIN E

The anti-carcinogenic properties of vitamin E are thought to be due in large part to its potent antioxidant activity – vitamin E is the major hydrophobic chain-breaking antioxidant that protects membrane lipids, including polyunsaturated fatty acids, from oxidation [7]. Interestingly, different vitamin E forms exhibit preferential affinity for reactive species. For example, although α-tocopherol is considered the most biologically active inhibitor of lipid peroxidation, γ-tocopherol is superior in scavenging reactive nitrogen oxide species [8, 9]. Data from mechanistic studies

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show that vitamin E acts synergistically with other antioxidant nutrients *in vitro*. For example, vitamin C and various flavonoids have been reported to regenerate α-tocopherol from α-tocopheroxyl radicals, which are formed when the parent molecule reduces free radicals [10-12]. Synergy between antioxidants has also been observed in human prostate cancer cell lines, although the resulting effects may not be attributable to their antioxidant activity *per se*. For example, D-α-tocopheryl-succinate (VES), a redox-silent derivative of vitamin E that possesses unique anti-neoplastic properties, and methylseleninic acid (MSA) together are more potent inducers of apoptosis than either agent alone, as confirmed by modulated caspase expression [13]. In other experiments, lycopene and α-tocopherol more strongly inhibit cell proliferation than either agent alone [14], and combinations of vitamin E and vitamin C more markedly reduce cell growth and induce apoptosis than when administered individually, as measured by survivin protein expression and translocation of nuclear factor κB (NF-κB) and activator protein 1 (AP-1) to the nucleus [15].

α-tocopherol has several important physiological functions that are independent of its antioxidant activity, including inhibition of protein kinase C (PKC) activity, which plays an important role in cell proliferation, adhesion, immune responses, free radical production, and gene expression [7]. In addition, α-tocopherol has been shown to regulate the expression of several genes involved in growth, apoptosis, and inflammation, including (AP-1), cyclin D1, p53, α-tropomyosin, collagenase, cytokine interleukin-1-β (IL-1β), glycoprotein IIB, and intercellular adhesion molecule 1 (ICAM-1), as well as several antioxidant defense genes [16]. In human prostate carcinoma cell lines, VES has been shown to induce apoptosis via the Fas pathway [17] and to modulate cell-cycle arrest by up-regulating p27 [18] and decreasing expression of certain cyclins and cdks [19]. VES has also been found to inhibit prostate cancer cell invasiveness through reduction of secreted matrix metalloproteinase 9 (MMP-9) [20]. γ-tocopherol, as well as its primary metabolite, 2,7,8-trimethyl-2-(β-carboxyethyl)-6-hydroxych-roman (γ-CEHC), is able to decrease prostaglandin E_2 (PGE_2) synthesis via inhibition of the cyclooxygenase-2 (COX2) enzyme, and therefore possesses potentially important anti-inflammatory properties [21]. Furthermore, γ-tocopherol was shown to more effectively inhibit proliferation and to decrease cell cycle progression via reduction of cyclin levels in prostate carcinoma cell lines than α-tocopherol [22]. All forms of vitamin E have been shown to induce the pregnane X receptor (PXR), which plays an important role in xenobiotic detoxification [23). γ- and α-tocotrienols are the most effective activators of PXR gene expression *in vitro*, with α- and γ-tocopherols showing much lower affinity. Interestingly, PXR mediates the activation of cyctochrome P450 enzymes that are involved in vitamin E metabolism. Therefore, some vitamin E forms may induce their own degradation, in part, via the PXR nuclear receptor.

Vitamin E appears to interfere with hormone signaling, which is particularly relevant to prostate carcinogenesis. For example, experimental studies using the androgen-dependent LNCaP human prostate cancer cell line have shown that VES suppresses androgen receptor expression [24]. In addition, the antioxidant moiety of vitamin E (2,2,5,7,8-pentamethyl-6-chromanol, PMCol) inhibits androgen-stimulated transcriptional activity, most likely through direct blockage of the androgen receptor [25]. In a cross-sectional analysis conducted within a subset of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, baseline serum α-tocopherol levels were found to be inversely associated with concentrations of serum sex hormones, including androstenedione, testosterone, sex-hormone-binding globulin, and estrone [26]. Furthermore, men randomized to the α-tocopherol supplementation group had significantly lower serum androstenedione and testosterone concentrations than those in the placebo group, after controlling for baseline hormone levels [27].

GENES INVOLVED IN VITAMIN E TRANSPORT AND METABOLISM

All dietary tocopherols and tocotrienols are absorbed in the intestine and released into the circulation via chylomicrons. Catabolism of chylomicrons by lipoprotein lipase results in the transport of vitamin E-containing chylomicron remnants to the liver, where RRR-α-tocopherol is selectively incorporated into very low density lipoproteins (VLDL) and subsequently re-released into the bloodstream. Other vitamin E isomers, including γ-tocopherol, are metabolized in the liver by cytochrome P450 enzymes (CYP3A4, CYP3A5, and CYP4F2) and excreted through the bile or urine, although small quantities are distributed to peripheral tissues during chylomicron lipolysis [28-30].

α-tocopherol is the most abundant form of vitamin E in plasma and most tissues, including in the prostate [31]. γ-tocopherol is ingested in greater quantities than α-tocopherol in many countries, including the United States, but its concentration in serum is only 10% of that of α-tocopherol [32]. The specific physiological preference for α-tocopherol results from the activity of the hepatic α-tocopherol transfer protein (α-TTP), which selectively incorporates α-tocopherol into circulating lipoproteins [33]. *In vitro* studies have shown that α-TTP exhibits relative affinities (RRR-α-tocopherol=100%) of only 38%, 9%, and 2% for β-tocopherol, γ-tocopherol, and δ-tocopherol, respectively [34]. Rare insertion and deletion mutations in the gene encoding α-TTP are associated with severely reduced plasma and tissue concentrations of α-tocopherol in humans, which lead to ataxia with vitamin E deficiency (AVED) – a neurological disorder that is easily treated via supplementation with vitamin E [35]. Loss of α-TTP function has also been shown to severely reduce plasma and tissue α-tocopherol concentrations in mice (plasma and tissue α-tocopherol concentrations in TTPA -/- knockouts are only 5% and 2 – 20%, respectively, of those in TTPA +/+ wild-type mice), indicating that this protein is important for tocopherol transport in species other than humans [36].

Specific vitamin E regulatory mechanisms in peripheral tissues remain unclear. Recently, a novel protein that preferentially facilitates *intracellular* transport of α-tocopherol was identified and named tocopherol associated protein (TAP) [37, 38]. Although expressed ubiquitously, concentrations of this protein were highest in liver, prostate, and brain tissues. This binding protein may therefore play a crucial role in the delivery of α-tocopherol to the prostate. *In vitro* experiments have shown that TAP translocates from the

cytosol to the nucleus upon binding to α-tocopherol, and subsequently activates gene expression [38]. Other potential roles for TAP include mediating the transport of α-tocopherol to organelles such as the Golgi apparatus or mitochondria, and/or assisting with the assembly of secretory granules [39].

Ongoing research has identified several other genes that bind α-tocopherol with relatively high affinity. These include tocopherol binding protein (TBP), scavenger receptor class B type I (SR-B1), ATP-binding cassette transporter A1 (ABCA1), and plasma phospholipid transfer protein (PLTP) [32, 40]. Each of these genes may influence the transport and cellular uptake of vitamin E in peripheral tissues, although more research is needed to clarify their specific functions.

Common SNPs in genes encoding α-TTP, TAP, and other important proteins may affect the transport and delivery of α-tocopherol to the prostate, and ultimately impact cancer risk at this site. SNPs in these genes have not been well characterized, and have not been examined with respect to prostate cancer, or any other cancer site, thus far.

EPIDEMIOLOGIC STUDIES OF VITAMIN E AND PROSTATE CANCER

Twenty-eight distinct epidemiologic studies of vitamin E and prostate cancer have been published to date, including 10 case-control studies [41-50], six cohort studies [51-57], one case-cohort study [58], 10 nested case-control studies [59-67], and one supplementation trial [68]. The results from these studies are summarized in **Table 1**. The most convincing evidence for a protective effect of vitamin E on prostate cancer comes from the ATBC Study, in which statistically significant reductions in prostate cancer incidence (32%) and mortality (41%) were observed among male smokers randomized to receive 50 mg α-tocopherol supplements daily for 5 – 8 years (median = 6.1 years) [68]. Numerous observational studies indicate that total vitamin E (diet + supplements) [55], dietary vitamin E [42, 44, 45, 55], supplemental vitamin E [49, 58], circulating levels of α-tocopherol [41, 52, 53, 55, 60-62, 64] or circulating levels of γ-tocopherol [61, 64, 66] are associated with modest reductions in prostate cancer risk, although not all risk estimates are statistically significant. A potentially true protective effect of vitamin E on prostate cancer risk is supported by 1) the magnitude of the associations observed in most of these studies (most risk estimates ranged between 0.50 and 0.79); 2) the evidence of a dose-response relationship in several studies; and 3) the existence of several plausible biologic pathways and the consistency of the observational data with results from experimental models. However, the possibility of confounding cannot be ruled out in non-controlled observational studies. For example, vitamin E intake or vitamin E status could be serving as a marker of another factor or health-related behavior that causally reduces prostate cancer risk.

An inverse association between α-tocopherol and *advanced* forms of prostate cancer appears to be rather consistent among cigarette smokers [69]. In the Health Professionals Follow-Up Study, supplemental vitamin E was not associated with overall prostate cancer incidence, but did confer apparent protection against metastatic or fatal disease among the combination of current smokers and recent quitters (≥ 100 IU/day versus none, RR = 0.44 (95% CI = 0.18-1.07) [51]. No association was observed in never-smokers or former smokers in that study [51]. A cohort study conducted in Switzerland, although limited by a small number of cases, showed that low versus high plasma α-tocopherol levels (< 30.02 versus ≥ 30.02 μmol/liter, adjusted for lipids) increased the risk of fatal prostate cancer in smokers, but not in non-smokers [52, 53]. In a case-control study nested within the prospective Physician's Health Study, high versus low plasma α-tocopherol levels (> 14,441 versus < 8564 ng/mL) were more strongly inversely associated with aggressive than with total prostate cancers [60]. This association was more apparent among current or former smokers (quintile 5 versus quintile 1, OR = 0.51; 95% CI = 0.26-0.98) than among never smokers (quintile 5 versus quintile 1, OR = 0.84; 95% CI = 0.36-1.94). In the ATBC Study, α-tocopherol supplementation resulted in a greater reduction in prostate cancer incidence among longer term than among shorter term smokers (≥ 36 years of smoking = 43% reduction, < 36 years of smoking = 3% reduction, *p* interaction = 0.05) and among heavier than lighter smokers (≥ 20 cigarettes/day = 51% reduction, < 20 cigarettes/day = 25% reduction, *p* interaction = 0.15) [68]. Although cigarette smoking is not generally considered to be a risk factor for overall prostate cancer, it does appear to increase the risk of advanced or fatal disease [70]. One potential explanation for the apparent interaction between smoking and vitamin E with respect to prostate carcinogenesis is that carcinogenic substances present in cigarette smoke may accelerate the progression of prostate cancer, and that vitamin E helps stem smoking-induced transformation of latent to advanced disease. However, the precise sequence of events underlying such a potential mechanism is currently unknown.

Null associations (defined as statistically nonsignificant point estimates in the range of 0.80 to 1.20) between vitamin E and prostate cancer have been reported in numerous studies examining total vitamin E (diet + supplements) [48, 51, 54], dietary vitamin E [46-48, 50, 58], supplemental vitamin E, [56, 57], or circulating levels of total vitamin E [59, 66, 71], α-tocopherol [67, 71], or γ-tocopherol [60, 62, 66, 71]. There are several possible explanations for these null findings. Questionnaire-based measures may be limited in their ability to accurately capture vitamin E intake since this nutrient is widely distributed in many foods. Potentially significant contributors of vitamin E, including different vegetable oils, may therefore not be included on dietary questionnaires. Inadequate variation in vitamin E intake (from diet and/or supplements) within certain populations and limited statistical power may also have impeded the ability of previous studies to detect a potentially true inverse association between vitamin E and prostate cancer. Since prostate cancer develops over many years, a single measurement of vitamin E may not be representative of usual vitamin E intake or vitamin E status during the etiologically critical exposure period in the past. Moreover, prostate cancer varies considerably with respect to aggressive potential, and vitamin E may differentially affect

Table 1. Epidemiologic Studies of Vitamin E and Prostate Cancer

Author / Year	Location	Study Population[1]	Study Design[2]	Cases (n)	Vitamin E Measure	Risk Estimate[3] (95% CI[4]); *p* trend[5]
Hayes *et al.* (41), 1988	Netherlands	50 – 79 years old	Case-control (hosp)	134 total (94 clinical)	Serum α-tocopherol	Total cases[6] = 1.5 (CI not provided); *p* = 0.11 Clinical cases[6] = 1.7 (CI not provided); *p* = 0.09
Deneo-Pellegrini *et al.* (42), 1999	Uruguay	40 – 89 years old	Case-control (hosp)	175	Dietary vitamin E	0.6 (0.3-1.1); *p* = 0.03
Meyer *et al.* (43), 1997	Canada	≥ 45 years old	Case-control (hosp)	215 preclinical	Total vitamin E (diet + supplements)	1.46 (0.76-2.82); *p* = 0.43
Tzonou *et al.* (44), 1999	Greece	Mean age (cases) = 71.1 years	Case-control (hosp)	320	Dietary vitamin E	0.47[7] (0.23-0.96); *p* = 0.03[8]
Vlajinac *et al.* (45), 1997	Serbia	Mean age (cases) = 70.5 years	Case-control (hosp)	101	Dietary α-tocopherol	0.15 (0.05-0.53); *p* = 0.01
Andersson *et al.* (46), 1996	Sweden	< 80 years old	Case-control (pop)	526 total (296 advanced)	Dietary tocopherol	Total cases = 0.91 (0.64-1.28); *p* = 0.74 Advanced cases = 0.89 (0.60-1.33); *p* = 0.52
Jain *et al.* (47), 1999	Canada	Mean age (cases) = 69.8 years	Case-control (pop)	617	Dietary vitamin E	1.12 (0.81-1.55); *p* > 0.05
Key *et al.* (48), 1997	England	< 75 years old	Case-control (pop)	328 total (94 advanced)	Total vitamin E (diet + supplements)	Total cases = 0.85 (0.58-1.25); *p* = 0.41 Advanced cases = null association (data not provided)
					Dietary vitamin E	Total cases = 0.93 (0.63-1.37); *p* = 0.89 Advanced cases = null association (data not provided)
Kristal *et al.* (49), 1999	United States	40 – 64 years old	Case-control (pop)	697 total (503 early, 175 advanced)	Supplement	Total cases = 0.76 (0.54-1.08); *p* = 0.12 Early cases = 0.72 (0.48-1.06); *p* not provided Advanced cases = 0.71 (0.40-1.22); *p* not provided
Rohan *et al.* (50), 1995	Canada	Median age (cases) = 70.4 years	Case-control (pop)	207	Dietary vitamin E	Null association (data not provided)
Chan *et al.* (51), 1999	United States	40 – 75 years old	Cohort	1896 total non-stage A1 (522 extraprostatic, 232 metastatic / fatal)	Supplement	Total cases = 1.07 (0.95-1.20); *p* not provided Extraprostatic cases = 1.22 (0.98-1.52); *p* not provided Metastatic / fatal cases = 1.14 (0.82-1.59); *p* not provided
					Total vitamin E (diet + supplements)	Total cases = 1.00 (0.86-1.17); *p* not provided Extraprostatic cases = 0.96 (0.72-1.27); *p* not provided Metastatic / fatal cases = 0.89 (0.58-1.36); *p* not provided

Table 1 Continued

Author / Year	Location	Study Population[1]	Study Design[2]	Cases (n)	Vitamin E Measure	Risk Estimate[3] (95% CI[4]); *p* trend[5]
Eichholzer *et al.* (52, 53), 1996, 1999	Switzerland	20 – 79 years old	Cohort	30 fatal	Plasma α-tocopherol	Smokers = 3.26[6] (1.27-8.35) Nonsmokers = 0.76[6] (0.25-2.36)
Giovannucci *et al.* (54), 1995	United States	40 – 75 years old	Cohort	773 total non-stage A1	Total vitamin E (diet + supplements)	0.94 (0.75-1.17); *p* = 0.62
Hartman *et al.* (55), 1998	Finland	50 – 69 years old	Cohort	317	Total vitamin E (diet + supplements)	Within α-tocopherol supplemented group, 0.52 (0.29-0.95); *p* = 0.07
					Dietary vitamin E	0.65 (0.36-1.18); *p* = 0.21
					Dietary α-tocopherol	0.70 (0.44-1.31); *p* = 0.29
					Dietary γ-tocopherol	0.56 (0.32-0.98); *p* = 0.08
					Serum α-tocopherol	0.76 (0.42-1.37); *p* = 0.37
						Null associations in non-α-tocopherol supplemented group; null associations overall
Rodriguez *et al.* (56), 2004	United States	50 – 74 years old	Cohort	4281 total (668 advanced)	Supplement	Total cases = 1.04 (0.94-1.15); *p* = 0.32 Advanced cases = 0.96 (0.74-1.24); *p* = 0.95
Shibata *et al.* (57), 1992	United States	Mean age (cohort) = 74.9 years	Cohort	208	Supplement	1.00 (0.76-1.31)
Schuurman *et al.* (58), 2002	Netherlands	55 – 69 years old	Cohort (case-cohort)	642 total (210 advanced)	Supplement	Total cases = 0.70 (0.42-1.15) Advanced cases = 0.70 (0.33-1.49)
					Dietary vitamin E	Total cases = 0.94 (0.68-1.29); *p* = 0.42 Advanced cases = 0.96 (0.61-1.50); *p* = 0.57
Comstock *et al.* (59), 1991	United States	≥ 18 years old	Cohort (nested c-c)	103	Serum vitamin E	1.00[6] (CI not provided); *p* = 0.9
Gann *et al.* (60), 1999	United States	40 – 84 years old	Cohort (nested c-c)	578 total (259 aggressive)	Plasma α-tocopherol	Total cases = 1.06 (0.76-1.48); *p* = 0.70 Aggressive cases = 0.64 (0.38-1.07); *p* = 0.11
					Plasma γ-tocopherol	Total cases = 0.98 (0.71-1.35); *p* = 0.89 Aggressive cases = 1.00 (0.62-1.60); *p* = 0.96
Goodman *et al.* (62), 2003	United States	45 – 69 years old	Cohort (nested c-c)	205	Serum α-tocopherol	0.59 (0.34-1.04); *p* = 0.04
					Serum γ-tocopherol	0.86 (0.50-1.48); *p* = 0.57
Helzlsouer *et al.* (61), 2000	United States	Mean age (cases) = 66.4 years	Cohort (nested c-c)	117 total (69 advanced)	Plasma α-tocopherol	Total cases = 0.64 (0.30-1.36); *p* = 0.37
					Plasma γ-tocopherol	Total cases = 0.25 (0.09-0.68); *p* = 0.01 Advanced cases = stronger association (data not provided)

Table 1 Continued

Author / Year	Location	Study Population[1]	Study Design[2]	Cases (n)	Vitamin E Measure	Risk Estimate[3] (95% CI[4]); *p* trend[5]
Hsing *et al.* (71), 1990	United States	Median age (cases) = 71 years	Cohort (nested c-c)	103	Serum vitamin E (total tocopherol)	1.00 (0.37-2.68); *p* = 0.90
					Serum α-tocopherol	1.00 (0.09-3.45)
					Serum γ-tocopherol	1.17 (0.39-3.47)
Huang *et al.* (64), 2003	United States	Mean age (cases) = 54 years	Cohort (nested c-c)	182	Serum α-tocopherol	0.58 (0.31-1.06); *p* = 0.11
					Serum γ-tocopherol	0.77 (0.42-1.43); *p* = 0.30
Huang *et al.* (64), 2003	United States	Mean age (cases) = 66 years	Cohort (nested c-c)	142	Plasma α-tocopherol	0.78 (0.41-1.50); *p* = 0.46
					Plasma γ-tocopherol	0.21 (0.08-0.54); *p* = 0.001
Knekt *et al.* (65), 1988	Finland	≥ 15 years old	Cohort (nested c-c)	36	Serum α-tocopherol	1.44 (CI not provided); *p* = 0.58[8]
Nomura *et al.* (66), 1997	United States	52 – 74 years old	Cohort (nested c-c)	142	Serum total tocopherols	0.90 (0.5-1.9); *p* = 0.64
					Serum α-tocopherol	1.4 (0.7-2.9); *p* = 0.71
					Serum γ-tocopherol	0.7 (0.3-1.5); *p* = 0.27
Willett *et al.* (67), 1984	United States	30 – 69 years	Cohort (nested c-c)	11	Serum α-tocopherol	No risk estimate provided; case-control difference in α-tocopherol levels = -0.09 ± 0.19[9]
Heinonen *et al.* (68), 1998	Finland	50 – 69 years old	Trial	246 total (54 latent, 192 clinical)	Supplement	α-tocopherol intervention versus no α-tocopherol: Incidence in total cases = 32% (-47% to -12%) Incidence in latent cases = null association (data not provided) Incidence in clinical cases = 40% (-55% to - 20%)
				62 deaths		Mortality in total cases = 41% (-65% to –1%)

[1] Age range, mean / median age of cases, or mean age of full study population.
[2] Case-control (hosp) = hospital-based case-control study; case-control (pop) = population-based case-control study; cohort (case-cohort) = case-cohort study nested within a cohort study, cohort (nested c-c) = case-control study nested within a cohort study.
[3] All risk estimates are based on a comparison of the highest versus the lowest category of dietary or serum vitamin E, unless otherwise noted. For studies involving supplement use, risk estimates correspond to ever versus never use. Risk estimates correspond to the most fully adjusted multivariate models.
[4] 95% CI = 95 percent confidence interval.
[5] *p*-values for linear trend correspond to the most fully adjusted multivariate models, unless otherwise specified. *p*-values for trend do not apply to binary exposure variables.
[6] Risk estimate is based on a comparison of the lowest versus the highest category of vitamin E.
[7] Risk estimate is based on an increment equal to 1 standard deviation among the controls.
[8] *p*-value for trend from less than fully adjusted model since *p*-value from fully adjusted model was not provided.
[9] Mean ± standard error.

more aggressive versus less aggressive prostate cancers. Failure to account for these differences could potentially obscure important associations. Alternatively, the null associations reported in previous studies that have examined vitamin E with respect to prostate cancer risk may reflect a true lack of a causal association.

Positive associations between total vitamin E (diet + supplements) [43], supplemental vitamin E [51], or serum α-tocopherol [65, 66] and prostate cancer risk have been observed in only a small number of studies. Importantly, none of the positive associations reported in these studies approached statistical significance, which indicates that an adverse effect of vitamin E intake on prostate cancer development in the ranges derived from human diets and through supplementation is unlikely. Reported positive associations are not easily explained given considerable evidence from mechanistic studies supporting the anti-carcinogenic properties of vitamin E. It is possible that

previous positive findings are due to chance. A further, though improbable, possibility is that these results are due to confounding by concurrent use of other types of dietary supplements that may be contaminated by non-essential, potentially harmful trace elements such as cadmium [72], a known human carcinogen [73].

Three randomized clinical trials have been initiated that will examine the effect of supplemental vitamin E intake, alone or in combination with other vitamins and minerals, on the incidence of and mortality from prostate and other cancers. The largest is the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which is designed to investigate whether daily supplementation with vitamin E (400 mg α-tocopherol) and/or selenium (200 μg) for up to 12 years reduces the incidence of prostate cancer among 32,400 U.S. men [74]. The Physicians' Health Study (PHS) II randomized 15,000 physicians aged 55 years and older to vitamin E (400 IU of synthetic α-tocopherol), β-carotene, vitamin C, and multivitamins, alone and in combination, or a placebo on alternate days [75]. Individuals will be followed for five years. In contrast to the ATBC Trial, both SELECT and PHS II are testing *a priori* whether vitamin E reduces the risk of prostate cancer. The third trial – the SUpplementation en VItamines et Mineraux AntioXidants (SUVIMAX) Study – randomized over 12,000 French adult men and women (ages 35 – 60 years) to a multivitamin/ mineral supplement containing 30 mg of vitamin E or a placebo, and followed individuals for up to 8 years [76]. The trial is now complete, and results are expected to be available shortly. These trials should help clarify some of the inconsistencies observed in previous observational studies, and they may help establish or refute a causal relationship between vitamin E and prostate cancer. These results are particularly important considering that daily use of vitamin E supplements in the United States has increased almost 200% since 1987 [77]. This is the largest increase for any supplement that was examined in the U.S. National Health Interview Survey.

FUTURE RESEARCH DIRECTIONS

Although substantial laboratory data support a protective effect of α-tocopherol on prostate cancer risk, further research is needed in several areas. The precise biological mechanisms of action through which vitamin E exerts its effects on prostate carcinogenesis should continue to be investigated at the molecular, cellular, and tissue levels. Clearly, non-antioxidant functions of vitamin E, including modulation of immune function, induction of apoptosis, and interference with hormone production, play important physiological roles, and each needs to be further elucidated. The functional roles of TAP and other potentially important transport proteins require additional clarification. Common polymorphisms in α-TTP, TAP, and other relevant genes need to be identified, validated, and examined, since they might influence the transport and delivery of α-tocopherol to the prostate, and ultimately impact upon cancer risk at this site. Furthermore, polymorphisms in these genes might enable us to distinguish between individuals that vary in their response to vitamin E supplementation.

At the population level, results from ongoing, randomized, clinical trials, as well as findings from well-designed, prospective cohort studies that encompass comprehensive assessments of dietary vitamin E, supplemental vitamin E, and circulating tocopherol levels and large numbers of prostate cancer endpoints, will help clarify current inconsistencies in the literature. Special attention needs to be given to the role of vitamin E in the prevention of prostate cancer in men of African descent, a population that has not been adequately examined in previous studies. In addition, careful control of confounding by lifestyle and socioeconomic factors should be undertaken in future observational studies.

There is evidence supporting a specific protective effect of γ-tocopherol on prostate cancer risk. Thus, studies should distinguish between different vitamin E forms, such as α-tocopherol and γ-tocopherol. Because high doses of α-tocopherol, as are achievable through supplementation, are known to markedly decrease circulating levels of γ-tocopherol [78], supplementation with α-tocopherol alone might need to be carefully re-evaluated. This consideration may apply not only to supplementation trials, but also to the general population because a considerable proportion of U.S. adults currently consumes supplements containing α-tocopherol, but not γ-tocopherol [79]. Detailed information regarding the most effective dose, duration, and formulation of vitamin E necessary to prevent prostate cancer is also needed.

Prostate cancer varies significantly regarding its invasive potential, and vitamin E has been reported to be more strongly inversely related to advanced versus organ-confined prostate cancers. Thus, ongoing and future studies should consider total, organ-confined, advanced, and fatal prostate cancer as separate endpoints when evaluating the effect of vitamin E. Also, the possible benefit of vitamin E among smokers requires further research.

PUBLIC HEALTH RECOMMENDATION

Despite considerable advances in our understanding of the relationship between vitamin E and prostate cancer in recent years, the evidence regarding this association, while promising, is far from conclusive. Thus, additional research remains to further elucidate the role of tocopherols in prostate carcinogenesis. Recent evidence suggests that the apparent reduction in prostate cancer risk that may be achieved through vitamin E supplement use may be countered by an increase in all-cause mortality [80]. In a meta-analysis of 19 randomized, controlled trials, high-dose vitamin E ($\geq$ 400 IU/day) versus control was associated with a modest, though statistically significant 4% increase in risk of all-cause mortality. This dose is well below the Tolerable Upper Intake Level (UL) for vitamin E, which is set at 1000 mg/day of any form of supplemental α-tocopherol [1]. Thus, work will be needed to determine the risk-benefit trade-offs associated with supplemental vitamin E intake. In the meantime, the most prudent strategy for prostate cancer prevention with respect to vitamin E intake is to adhere to current U.S. dietary guidelines, which recommend eating a well-balanced diet that is rich in a variety of fruits, vegetables, and whole grains [81].

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